

RESPONSE

I. Rejection of Claims Under 35 U.S.C. § 101

The Advisory Action persists in rejecting all pending claims under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully maintain their traverse.

While Applicants do not wish to reiterate all previous evidence and arguments presented in Response to Paper nos. 9, 12, 14, 18 and 21, these positions are maintained and herein incorporated by reference in their entirety. Applicants respectfully submit that in the specification as filed, Applicants asserted that the sequences of the present invention encode a novel human CD20 antigen-like membrane protein, that plays a role in connective tissue disorders (specification at page 12, line 9). The CD20 antigen is a transmembrane protein on pre-B and mature B lymphocytes. CD20 functions as a calcium-permeable cation channel involved in signal transduction and regulates early steps in B lymphocyte activation. The molecule is not shed from the cell surface, and is not internalized upon antibody binding. CD20 is found on over 90 percent of B-cell lymphomas, as well as other lymphoid tumors of B cell origin. CD20 is the target of the humanized anti-CD20 monoclonal antibody therapy known as Rituxan® (Rituximab) an FDA approved treatment for B-cell lymphomas and shows some efficacy in treating other B-cell malignancies in humans.

The sequences of the present invention encode a CD20-like protein now known to those skill in the art as Membrane-spanning 4-domains subfamily A member 5 (MS4A5) (testis-expressed transmembrane 4 protein) (CD20 antigen-like 2)" (as evidenced in Applicants' previous response). Members of this protein family are known to those of skill in the art to be characterized by common structural features and similar intron/exon splice boundaries. This protein, like its related family members, functions in signal transduction (**Exhibits A and B**). Additionally, the gene encoding this protein, MS4A5, is recognized by those of skill in the art to be localized to position 11q12, among a cluster of family members. This is identical to the position identified in Applicants' previous response regarding the utility of the sequences of the present invention in chromosome mapping and the accompanying exhibit.

Furthermore, as previously submitted, Systemic Sclerosis is a chronic inflammatory connective-tissue disorder characterized by fibrosis of skin and viscera in humans. Those of skill in the art

recognized the role of natural killer (NK) cells in the pathophysiology of such connective tissue disorders prior to Applicants' filing (see, for example, Wanchu, *et al.*, Lack of natural killer cell augmentation *in vitro* by human interferon gamma in a subset of patients with systemic sclerosis, Pathobiology, 63(5):288-92, 1995: previously submitted as Exhibit A in Applicants' Response to the Final Action). The relationship between NK cells and, for example, systemic sclerosis has been verified by those of skill in the art, see Ercole *et al.*, 2003 (Analysis of lymphocyte subpopulations in systemic sclerosis, J Invest Allergol Clin Immunol. 13(2):87-93: previously submitted as Exhibit B in Applicants' Response to the Final Action), who found that patients with diffuse and late-stage disease had smaller percentages of NK cells. Thus, clearly those of skill in the art recognize the role of NK cells in connective tissue disorders such as Systemic Sclerosis.

In previous Responses, Applicants have described Applicants' findings involving the analysis of transgenic "knockout" mice (which were described in the specification, at least on page 2, lines 17-20) that were subject to a comprehensive medical work-up using an integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject. Disruption of the mouse ortholog of the claimed human sequences and thus elimination of the protein they encode, resulted in an increase in the level of natural killer (NK) cells that were detected in the blood of animals in which this gene activity had been disrupted. As evidence that Applicants' previous assertion that these findings and their significance would be recognized by those of skill in the art, Applicants herewith enclose a Declaration under 37 C.F.R. § 1.132 by Tamas Oravecz, Ph.D., the Director of Immunology at Lexicon Genetics Incorporated, describing these findings and their significance to those of skill in the art. This Declaration clearly indicates that the protein encoded by the murine ortholog of the human sequences of the present invention plays a role in NK cell regulation. And clearly those of skill in the art recognize and would accept this as *in vivo* evidence that the protein encoded by the claimed human sequences also have a role in regulating NK cell levels and that NK cells are known to play a role in human connective tissue disorders such as Systemic Sclerosis. Therefore, Applicants' assertion in the specification as filed, that the molecules of the present invention are involved in human connective tissue disorders like Systemic Sclerosis would be accepted and deemed as credible by those of skill in the art. Therefore, as a biologically validated signal transduction protein involved in the regulation of NK cell levels and given the recognized role of NK cells in human connective tissue disorders like Systemic Sclerosis, the molecules of the present invention have well-

recognized real world substantial and specific utility. Those of skill in the art would clearly recognize the utility of the present invention in addressing connective tissue disorders as well as be enabled to make and use the present invention without undue experimentation. Thus, the present invention clearly has credible specific and substantial real world utility and meets all of the requirements of 35 U.S.C. § 101.

Thus, in summary, Applicants have asserted in the specification that the sequences of the present invention encode a novel human CD20 antigen-like membrane protein, that plays a role in connective tissue disorders (specification at page 12, line 9). Applicants have supplied evidence that those of skill in the art have also recognized the protein encoded by the claimed sequences as a CD20 antigen-like membrane protein (MS4A5), a member of a family of proteins known to function in signal transduction, with the same tissue testis specific expression pattern described in the specification (first paragraph of Section 5, at or about page 3, line 5). Thus, clearly, Applicants' assertions regarding the protein encoded by the sequences of the present invention were credible. Furthermore, Applicants have provided evidence that disruption of the murine ortholog of the human protein encoded by the claimed sequences resulted in increased NK cell levels in mice and that NK cell levels are known by those of skill in the art to be critical components in human connective tissue disorders. Thus, the role of the human protein encoded by the sequences of the present invention and its association with human connective tissue disease, as asserted in the specification, is also supported by the evidence provided, further indicating that the present invention is in full compliance with the provisions of 35 U.S.C. § 101, and the rejection of the pending claims should be withdrawn.

II. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action also rejects the pending claims under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as the sequences of the present invention have been shown to have a specific, substantial, credible and well established utility, as detailed in section I above, Applicants therefore respectfully request that the rejection of claims under 35 U.S.C. § 112, first paragraph, be withdrawn.